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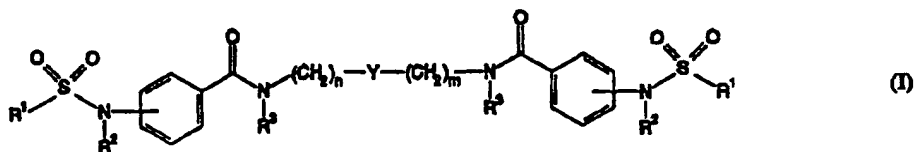
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(54) Title: BIS-ARYLSULFONYLAMINO BENZAMIDE DERIVATIVES AND THE USE THEREOF AS FACTOR Xa INHIBITORS



(57) Abstract

The present invention is directed to non-peptidic factor Xa inhibitors which are useful for the treatment of arterial and venous thrombotic occlusive disorders, inflammation, cancer, and neurodegenerative diseases. The factor Xa inhibitors provide compounds of structure (I), wherein each R<sup>1</sup> is independently one of alkyl, substituted alkyl, cycloalkyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl; each R<sup>2</sup> and R<sup>3</sup> is independently one of hydrogen, alkyl, aryl or arylalkyl; Y is a bond, or is one of -(CH<sub>2</sub>)<sub>p</sub>, cycloalkyl, aryl or C<sub>2-10</sub> heterocycle; and m, n and p are each independently 1 to 10.

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## Bis-Arylsulfonylamin benzamide Derivatives and the Use Thereof as Factor Xa Inhibitors

### *Field of the Invention*

5       The present invention relates to compounds that are inhibitors of  
thrombin production via factor Xa inhibition, their pharmaceutically  
acceptable salts, and pharmaceutically acceptable compositions thereof. The  
compounds and compositions are useful in the treatment of arterial and  
venous thrombotic occlusive disorders, inflammation and cancer.

### *Background of the Invention*

10       The serine protease thrombin occupies a central role in hemostasis  
and thrombosis (Tapparelli *et al.*, *Trends in Pharmacological Sciences*  
14:366-376 (1993); Lefkovits and Topol, *Circulation* 90(3):1522-1536  
(1994); Harker, *Blood Coagulation and Fibrinolysis* 5 (Suppl 1):S47-S58  
15       (1994)). Activation of the coagulation cascade through either the intrinsic  
pathway (contact activation) or the extrinsic pathway (activation by exposure  
of plasma to a non-endothelial surface, damage to vessel walls or tissue  
factor release) leads to a series of biochemical events that converge on  
thrombin. Thrombin cleaves fibrinogen ultimately leading to a hemostatic  
plug (clot formation), potently activates platelets through a unique proteolytic  
20       cleavage of the cell surface thrombin receptor (Coughlin, *Seminars in*  
*Hematology* 31(4):270-277 (1994)), and autoamplifies its own production  
through a feedback mechanism.

25       As a multifactorial protein, thrombin induces a number of effects on  
platelets, endothelial cells, smooth muscle cells, leukocytes, the heart, and  
neurons (Tapparelli *et al.*, *Trends in Pharmacological Sciences* 14:366-376  
(1993); Church and Hoffman, *Trends in Cardiovascular Medicine* 4(3):140-  
146 (1993)). Platelet activation leads to shape change and aggregation as  
well as the synthesis, release and secretion of vasoactive substances and  
lysosomal enzymes. Endothelial cell activation results in the secretion of

stimulatory agents leading to increased vascular permeability and adhesiveness for mononuclear cells, one consequence of which is extravasation of leukocytes at the site of thrombin generation. Thrombin induces fibroblast and smooth muscle cell proliferation suggesting that thrombin plays a key role in lesion development following vascular damage. Enhanced automaticity and prolongation of repolarization have been observed in cardiac myocytes showing sensitivity to thrombin. Normal neuronal development has been shown also to be influenced by thrombin. Thus, inhibitors of thrombin function have therapeutic potential in a host of cardiovascular and non-cardiovascular diseases, including: myocardial infarction; unstable angina; stroke; restenosis; deep vein thrombosis; disseminated intravascular coagulation caused by trauma, sepsis or tumor metastasis; hemodialysis; cardiopulmonary bypass surgery; adult respiratory distress syndrome; endotoxic shock; rheumatoid arthritis; ulcerative colitis; induration; metastasis; hypercoagulability during chemotherapy; Alzheimer's disease; and Down's syndrome.

To date only three classes of compounds (heparins, low-molecular weight heparins, and coumarins, such as warfarin) have been used in anticoagulant therapy. Each class has severe limitations and liabilities (Weitz and Hirsh, *Journal of Laboratory Clinical Medicine* 122:364-373 (1993); Raj *et al.*, *The American Journal of the Medical Sciences* 307(2):128 (1994)). All three classes indirectly inhibit thrombin. Heparin and low-molecular weight heparins augment antithrombin III and/or heparin cofactor II inhibition of thrombin, whereas coumarins inhibit vitamin K-dependent post-translational modification. Close monitoring and titration of therapeutic doses is required when employing these agents due to patient variability. Hemorrhagic complications due to bleeding are an encountered side effect. In fact, bleeding remains as the most common side effect of long term oral anticoagulant therapy. Lack of activity in arterial thrombosis in the case of heparin is due to its inability to inhibit clot bound thrombin.

Lack of oral activity in the case of heparins and low-molecular weight heparins preclude their use for chronic administration.

Direct thrombin inhibitors of various structural classes have been identified recently (Tapparelli *et al.*, *Trends in Pharmacological Sciences* 14:366-376 (1993); Claeson, *Blood Coagulation and Fibrinolysis* 5:411-436 (1994); Lefkovits and Topol, *Circulation* 90(3):1522-1536 (1994)). Representative compounds that act by inhibiting the active site of thrombin include the  $\alpha$ -chloroketone D-phenylalanyl-L-prolyl-L-arginyl chloromethylketone (PPACK), the boroarginine DUP714, the peptide arginal GYK114766, the cyclic peptides cyclotheonamides A and B, the benzamidine NAPAP, and the arylsulphonylarginine argatroban. The thrombin inhibitory peptides hirudin and hirulogs additionally span through the active and exosite domains of thrombin. The peptide hirugen and single-stranded DNA aptamers inhibit thrombin through exosite occupancy. These classes of antithrombotic agents still suffer from one or more of the following liabilities: (1) poor oral bioavailability due to the peptidic or oligonucleotidic nature of these agents, or high molecular weight or charged nature of the agents; (2) excessive bleeding complications; (3) poor selectivity towards thrombin versus other serine proteases (which may lead to severe and sometimes fatal hypotension and respiratory depression in animal models); (4) liver toxicity; or (5) cost effectiveness.

An alternative approach for inhibiting thrombin function is to inhibit factor Xa. Factor Xa associates with factor Va and calcium on a phospholipid membrane thereby forming a prothrombinase complex. This prothrombinase complex then converts prothrombin to thrombin (Claeson, *Blood Coagulation and Fibrinolysis* 5:411-436 (1994); Harker, *Blood Coagulation and Fibrinolysis* 5 (Suppl 1):S47-S58 (1994)). Inhibitors of factor Xa are thought to offer an advantage over agents that directly inhibit thrombin since direct thrombin inhibitors still permit significant new thrombin generation (Lefkovits and Topol, *Circulation* 90(3):1522-1536 (1994); Harker, *Blood Coagulation and Fibrinolysis* 5 (Suppl 1):S47-S58

(1994)). Indeed, continuous generation of new thrombin rather than reexposure of preformed clot-bound thrombin is thought to be responsible in part for the phenomenon of reocclusion since markers of thrombin generation have been found to increase during and after thrombolytic treatment for myocardial infarction. Thus, it is now believed that increased thrombin activity associated with thrombolysis is due at least in part to new thrombin generation.

Specific protein factor Xa inhibitors, such as the leech-derived, 119-amino acid protein antistasin and the soft tick derived protein TAP (tick anticoagulant peptide) accelerated clot lysis and prevented reocclusion when given as adjuncts to thrombolysis (Mellott *et al.*, *Circulation Research* 70:1152-1160 (1992); Sitko *et al.*, *Circulation* 85:805-815 (1992)). U.S. Patent No. 5,385,885, issued January 31, 1995, discloses smooth muscle cell proliferation inhibitory activity of both TAP and antistasin. Additionally, TAP and antistasin have been shown to reduce experimental restenosis. These results suggest that factor Xa may play a role in the restenosis process through its effects upon thrombus formation or through its mitogenic potential (Ragosta *et al.*, *Circulation* 89:1262-1271 (1994)). The peptide ecotin is another selective, reversible, tight-binding inhibitor of factor Xa that exhibits potent anticoagulant activity (Seymour *et al.*, *Biochemistry* 33:3949-3959 (1994); PCT Published Application WO 94/20535, published September 14, 1994). Ixodidae, argasin, and ancyllostomatin are other representative peptidic factor Xa inhibitors isolated from animals that feed on blood (Markwardt, *Thrombosis and Hemostasis* 72:477-479 (1994)).

Non-peptide diamidino derivatives, such as (+)-(2S)-2-[4-[(3S)-1-acetimidoyl-3-pyrrolidinyl]oxy]phenyl]-3-[7-amidino-2-naphthyl]propanoic acid hydrochloride pentahydrate (DX-9065a), exhibit anticoagulant activity (Tidwell *et al.*, *Thrombosis Research* 19:339-349 (1980); Yamazaki *et al.*, *Thrombosis and Hemostasis* 72:393-395 (1994); Hara *et al.*, *Thrombosis and Hemostasis* 71:314-319 (1994); Nagahara *et al.*, *Journal of Medicinal Chemistry* 37:1200-1207 (1994)). Synthetic amidino derivatives of

phenylalanine and cycloheptanone have also shown potent factor Xa inhibition (Sturzebecher *et al.*, *Thrombosis Research* 54:245-252 (1989)).

PCT Published Application WO 94/13693, published June 23, 1994, discloses peptide analogs containing an aldehyde grouping. The application discloses that the analogs have substantial potency and specificity as inhibitors of mammalian factor Xa.

PCT Published Applications WO 93/15756, published August 19, 1993, and WO 94/17817, published August 18, 1994, disclose peptidyl arginine aldehydes that exhibit factor Xa and/or thrombin inhibitory activity.

PCT Published Applications WO 94/20526, published September 15, 1994, discloses peptide derivatives having a C-terminal boronic acid group. The application discloses that these peptide derivatives possess protein-inhibiting activity and are potent thrombin inhibitors.

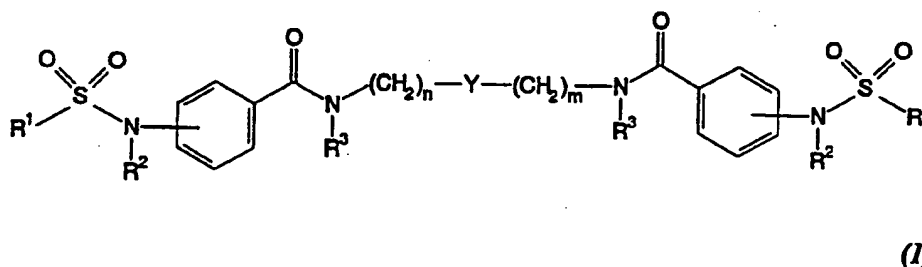
### *Summary of the Invention*

The present invention is directed to novel bis-arylsulfonylaminobenzamide derivatives having the Formula I (below). The compounds are formed by coupling arylsulfonylaminophenalkanoic acids with a diamine. Thus, also provided is a process for preparing compounds of Formula I.

The novel compounds of the present invention exhibit antithrombotic activity via factor Xa inhibition. Also provided is a method of treating thrombosis, ischemia, stroke, restenosis or inflammation in a mammal in need of such treatment comprising administering to said mammal an effective amount of a compound of Formula I. Further provided is a pharmaceutical composition comprising a compound of Formula I and one or more pharmaceutically acceptable carriers or diluents.

### *Detailed Description of the Preferred Embodiments*

The present invention provides novel compounds having the Formula I:



wherein

each  $R^1$  is independently one of alkyl, substituted alkyl, cycloalkyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl;

each  $R^2$  and  $R^3$  is independently one of hydrogen, alkyl, aryl or arylalkyl;

$Y$  is a bond, or is one of  $-(CH_2)_p-$ , cycloalkyl, aryl or  $C_{2-10}$  heterocycle; and

$m$ ,  $n$  and  $p$  are each independently 1 to 10.

Preferred compounds of the present invention are those of Formula I wherein each  $R^1$  is independently one of  $C_{6-12}$ aryl or  $C_{1-8}$ alkyl; each  $R^2$  and  $R^3$  is independently one of hydrogen,  $C_{1-8}$ alkyl or  $C_{6-12}$ aryl;  $Y$  is a bond, or is one of  $-(CH_2)_p-$ ,  $C_{3-8}$  cycloalkyl,  $C_{6-12}$  aryl or a 5 to 6 membered ring heterocycle; and  $m$ ,  $n$  and  $p$  are each 1 to 5.

Most preferred are compounds of Formula I wherein each  $R^1$  is the same and is either phenyl or naphthyl; each  $R^2$  is the same and is one of hydrogen,  $C_{1-5}$  alkyl, phenyl or naphthyl; each  $R^3$  is the same and is one of hydrogen,  $C_{1-5}$  alkyl, phenyl or naphthyl;  $Y$  is a bond, or is one of

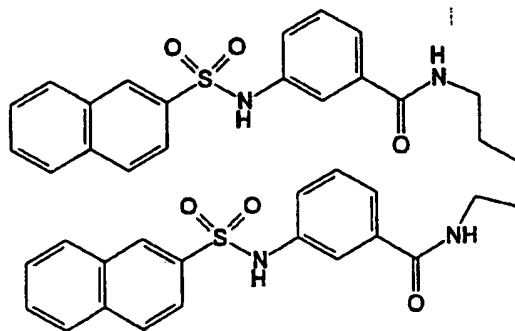


$-(CH_2)_p-$ ,  $C_{3-8}$  cycloalkyl,  $C_{6-10}$  aryl or 1,4-piperaziny; and m, n and p are each independently 1 to 5.

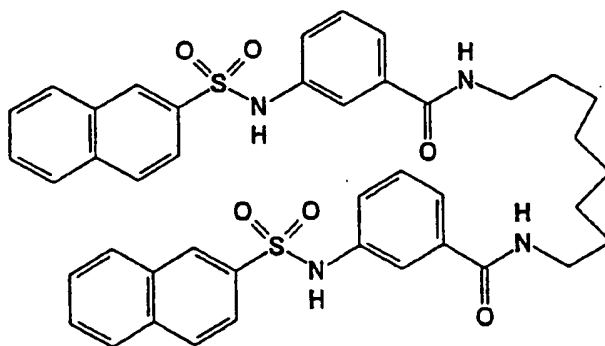
Preferred heteroaryl groups in reference to  $R^1$  include pyridinyl, thienyl, chromenyl, benzoxazolyl, quinazoliny, quinolinyl and tetrahydroquinolinyl.

In general, any heterocyclic diamine may be employed to form compounds having a variety of heterocyclic groups at position Y. Examples of useful heterocyclic radicals are listed herein. Heteroaryl groups meeting the basic definition of "heterocycle" given herein may also be employed as the heterocycle Y.

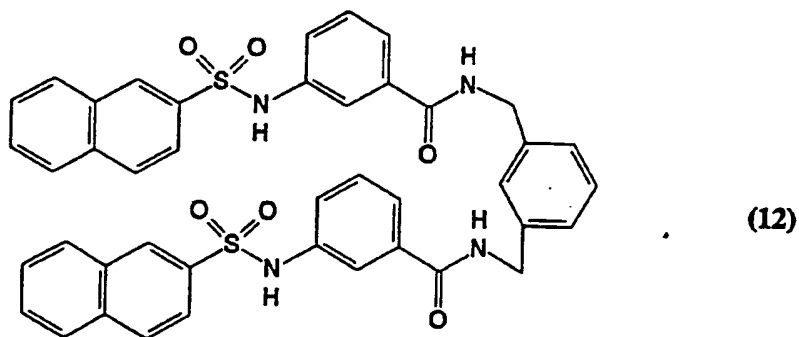
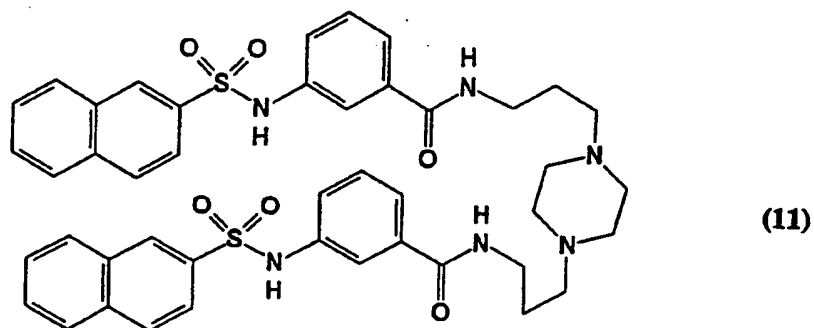
The most preferred compounds include those compounds wherein each  $R^1$  is 2-naphthyl, each  $R^2$  and  $R^3$  is each hydrogen, and Y is a bond, 1,4-substituted piperaziny, or 1,3-substituted phenyl. Thus, compounds having the following structures are most preferred:



(9)



(10)



The term "alkyl" as employed herein includes both straight and branched chain radicals of up to 12 carbons, preferably 1-8 carbons, such as methyl, ethyl, propyl, isopropyl, butyl, *t*-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethylpentyl, nonyl, decyl, undecyl, dodecyl and the various branched chain isomers thereof.

The term "substituted alkyl" as employed herein includes alkyl groups as defined above that have one, two or three halo substituents, or one  $C_{6-10}$  aryl,  $C_{1-6}$  alkyl( $C_{6-10}$ ) aryl, halo( $C_{6-10}$ ) aryl,  $C_{3-8}$  cycloalkyl,  $C_{1-6}$  alkyl( $C_{3-8}$ ) cycloalkyl,  $C_{2-8}$  alkenyl,  $C_{2-8}$  alkynyl, hydroxy and/or carboxy.

The term "cycloalkyl" as employed herein includes saturated cyclic hydrocarbon groups containing 3 to 12 carbons, preferably 3 to 8 carbons, which include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl and cyclododecyl, any of which groups may be

substituted with substituents such as halogen, C<sub>1-6</sub>alkyl, alkoxy and/or hydroxy group.

The term "aryl" as employed herein by itself or as part of another group refers to monocyclic or bicyclic aromatic groups containing from 6 to 12 carbons in the ring portion, preferably 6-10 carbons in the ring portion, such as phenyl, naphthyl or tetrahydronaphthyl.

The term "substituted aryl" as employed herein includes aryl groups, as defined above, that include one or two substituents on either the phenyl or naphthyl group such as C<sub>1-6</sub>alkyl, C<sub>3-8</sub>cycloalkyl, C<sub>1-6</sub>alkyl(C<sub>3-8</sub>)cycloalkyl, C<sub>2-8</sub>alkenyl, C<sub>2-8</sub>alkynyl, cyano, amino, C<sub>1-6</sub>alkylamino, di(C<sub>1-6</sub>)alkylamino, benzylamino, dibenzylamino, nitro, carboxy, carbo(C<sub>1-6</sub>)alkoxy, trifluoromethyl, halogen, C<sub>1-6</sub>alkoxy, C<sub>6-10</sub>aryl(C<sub>1-6</sub>)alkoxy, hydroxy, C<sub>1-6</sub>alkylthio, C<sub>1-6</sub>alkylsulfinyl, C<sub>1-6</sub>alkylsulfonyl, C<sub>6-10</sub>arylthio, C<sub>6-10</sub>arylsulfinyl and/or C<sub>6-10</sub>arylsulfonyl.

The term "aralkyl" or "arylalkyl" as used herein by itself or as part of another group refers to C<sub>1-6</sub>alkyl groups as discussed above having an aryl substituent, such as benzyl.

The terms "alkoxy," or "aralkoxy" includes any of the above alkyl or aralkyl groups linked to an oxygen atom.

The term "halogen" or "halo" as used herein by itself or as part of another group refers to chlorine, bromine, fluorine or iodine with chlorine being preferred.

The term "alkenyl" by itself or as part of another group as employed herein includes a carbon chain by itself or as part of another group of up to 16 carbons, preferably 2 to 10 carbons, containing one double bond such as propenyl, 2-butenyl, 3-butenyl, 2-pentenyl, 4-pentenyl and the like, and may include a halogen substituent such as I, Cl, or F.

The term "alkynyl" by itself or as part of another group as employed herein includes a carbon chain of up to 16 carbons, preferably 2 to 10 carbons, containing one triple bond such as 2-propynyl, 2-butynyl, 3-butynyl and the like.

5 The term "heterocycle" as employed herein refers to groups having 2 to 10 carbon atoms and having one or more 4, 5, 6, or 7 member saturated or unsaturated rings containing 1, 2, or 3 oxygen, nitrogen or sulfur heteroatoms (where examples of heterocyclic radicals are: tetrahydrofuran, 1,4-dioxane, 1,3,5-trioxane, pyrrolidine, piperidine, piperazine, imadazoline, isoindoline, chromane, isochromane, pyrazolidine, quinuclidine, pyridine, pyrrole, oxazole, indole, purine, pyrimidine, 1,3-dithiane, azetidine, tetrahydropyran, imidazole, thiazole, isoxazole, pyrazole, quinoline, cytosine, thymine, uracil, adenine, guanine, pyrazine, 1-methyl-1,4-  
10 dihydronicotine, picolinic acid, picoline, furoic acid, furfural, furfuryl alcohol, carbazole, isoquinoline, 3-pyrroline, thiophene, furan, hexamethyleneimine,  $\epsilon$ -caprolactone,  $\epsilon$ -caprolactam, omega-thiocaprolactam, and morpholine).

15 The term "heteroaryl" as employed herein refers to groups having 3 to 14 ring atoms; 6, 10 or 14  $\pi$  electrons shared in a cyclic array; and containing carbon atoms and 1, 2 or 3 oxygen, nitrogen or sulfur heteroatoms (where examples of heteroaryl groups are: thienyl, benzo[b]thienyl, naphtho[2,3-b]thienyl, thianthrenyl, furyl, pyranlyl, isobenzofuranyl, benzoxazolyl, chromenyl, xanthenyl, phenoxathiinyl, 2H-pyrrolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, 20 pyridazinyl, indoliziny, isoindolyl, 3H-indolyl, indolyl, indazolyl, purinyl, 4H-quinoliziny, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, quinazoliny, cinnoliny, pteridinyl, 4aH-carbazolyl, carbazolyl,  $\beta$ -carbolinyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl, phenazinyl, isothiazolyl, phenothiazinyl, isoxazolyl, furazanyl and phenoxazinyl groups).

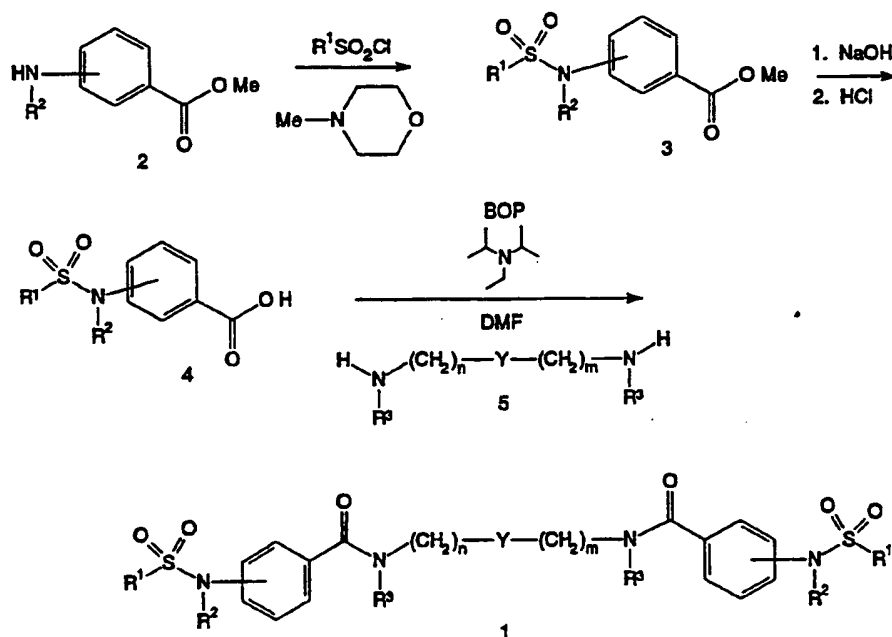
25 The terms "substituted heteroaryl" or "optionally substituted heteroaryl," used in reference to R<sup>1</sup>, refer to aryl groups, as defined above, having one or more substituents selected from halogen, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, carboxy, amino, C<sub>1-6</sub>alkylamino and/or di(C<sub>1-6</sub>)alkylamino.

30 The term "bond" as employed herein refers to a carbon to carbon single, double or triple bond.

The term "BOP" as employed herein refers to benzotriazol-1-yloxy-tris-(dimethylamino)phosphonium hexafluorophosphate.

The compounds of the present invention may be prepared by standard techniques as outlined in Scheme I.

### Scheme I



wherein  $R^1$ ,  $R^2$ ,  $R^3$ , Y, m and n are defined as above.

An aminobenzoic acid ester (that is optionally N-substituted) 2 is treated with an appropriate sulfonyl chloride under standard conditions to provide a N-sulfonylated derivative 3. Useful solvents for this step include methylene chloride, tetrahydrofuran, acetonitrile and dimethylformamide. The reaction proceeds at ambient temperature using a weak base, such as N-methylmorpholine, triethylamine or lutidine. Hydrolysis of 3 with aqueous hydroxide, preferably at elevated temperature for a short time followed by acidification with aqueous acid such as 2 N HCl gives the corresponding carboxylic acid 4. The final product is formed by coupling the carboxylic

acid 4 with a diamine 5 using well-known peptide coupling procedures. Reagents for the coupling step include, most preferably, Castro's reagent (BOP)/diisopropylethylamine, or alternatively, hydroxybenzotriazole (HOBT), hydroxysuccinimide, 1,3-dicyclocarbodiimide (DCC), carbonyldiimidazole (CDI), isobutylchloroformate/ $\text{NEt}_3$ , or diphenylphosphorylazide (DPPA)/ $\text{NEt}_3$ . The coupled dimeric product is the major product after usual workup.

Unsymmetrical products can be formed by employing a mixture of two distinct carboxylic acids (4), and thereafter separating unsymmetrical product from dimeric product. More preferably, one of the amino groups of the diamine reactant is first protected with an amino protecting group, such as phenylmethoxycarbonyl (Cbz) or *t*-butyloxycarbonyl (BOC). See Greene, T.W., *Protecting Groups in Organic Synthesis*, John Wiley, New York (1981). Thereafter, a first carboxylic acid can be condensed with the mono-protected diamine. The amino-protecting group is subsequently removed and the resulting intermediate is reacted with a second carboxylic acid to form a diarylsulfonylaminobenzamide derivative.

The compounds of the present invention are distinguished by their ability to preferentially inhibit factor Xa in comparison to thrombin and/or plasmin. As factor Xa inhibitors, the compounds of the present invention inhibit thrombin production. Therefore, the compounds are useful for the treatment or prophylaxis of states characterized by abnormal venous or arterial thrombosis involving either thrombin production or action. These states include, but are not limited to, deep vein thrombosis; disseminated intravascular coagulopathy which occurs during septic shock, viral infections, and cancer; myocardial infarction; stroke; coronary artery bypass; hip replacement; and thrombus formation resulting from either thrombolytic therapy or percutaneous transluminal coronary angioplasty (PCTA). The compounds of the present invention may also be used as an anticoagulant in extracorporeal blood circuits. By virtue of the effects of both factor Xa and thrombin on a host of cell types, such as smooth muscle cells, endothelial

cells and neutrophils, the compounds of the present invention find additional use in the treatment or prophylaxis of adult respiratory distress syndrome; inflammatory responses, such as edema; reperfusion damage; atherosclerosis; and restenosis following an injury such as balloon angioplasty, atherectomy, and arterial stent placement.

The compounds of the present invention may be useful in treating neoplasia and metastasis as well as neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease.

The compounds of the present invention may be used in combination with thrombolytic agents such as tissue plasminogen activator, streptokinase, and urokinase. Additionally, the compounds of the present invention may be used in combination with other antithrombotic or anticoagulant drugs such as, but not limited to, fibrinogen antagonists and thromboxane receptor antagonists.

The compounds of the present invention may be administered in an effective amount within the dosage range of about 0.1 to about 500 mg/kg, preferably between 0.1 to 10 mg/kg body weight, on a regimen in single or 2-4 divided daily doses.

The pharmaceutical compositions of the invention can be administered to any animal that can experience the beneficial effects of the compounds of the invention. Foremost among such animals are humans, although the invention is not intended to be so limited.

The pharmaceutical compositions of the present invention can be administered by any means that achieve their intended purpose. For example, administration can be by parenteral, subcutaneous, intravenous, intramuscular, intraperitoneal, transdermal, buccal, or ocular routes. Alternatively, or concurrently, administration can be by the oral route. The dosage administered will be dependent upon the age, health, and weight of the recipient, kind of concurrent treatment, if any, frequency of treatment, and the nature of the effect desired.

In addition to the pharmacologically active compounds, the new pharmaceutical preparations can contain suitable pharmaceutically acceptable carriers comprising excipients and auxiliaries that facilitate processing of the active compounds into preparations that can be used pharmaceutically. The pharmaceutical preparations of the present invention are manufactured in a manner that is, itself, known, for example, by means of conventional mixing, granulating, dragee-making, dissolving, or lyophilizing processes. Thus, pharmaceutical preparations for oral use can be obtained by combining the active compounds with solid excipients, optionally grinding the resulting mixture and processing the mixture of granules, after adding suitable auxiliaries, if desired or necessary, to obtain tablets or dragee cores.

Suitable excipients are, in particular, fillers such as saccharides, for example, lactose or sucrose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example, tricalcium phosphate or calcium hydrogen phosphate, as well as binders, such as, starch paste, using, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, tragacanth, methyl cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, and/or polyvinyl pyrrolidone. If desired, disintegrating agents can be added, such as, the above-mentioned starches and also carboxymethyl-starch, cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof, such as, sodium alginate. Auxiliaries are, above all, flow-regulating agents and lubricants, for example, silica, talc, stearic acid or salts thereof, such as, magnesium stearate or calcium stearate, and/or polyethylene glycol. Dragee cores are provided with suitable coatings that, if desired, are resistant to gastric juices. For this purpose, concentrated saccharide solutions can be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, polyethylene glycol, and/or titanium dioxide, lacquer solutions and suitable organic solvents or solvent mixtures. In order to produce coatings resistant to gastric juices, solutions of suitable cellulose preparations, such as, acetylcellulose phthalate or hydroxypropylmethylcellulose phthalate, are used. Dye stuffs or pigments can be added to the



tablets or dragee coatings, for example, for identification or in order to characterize combinations of active compound doses.

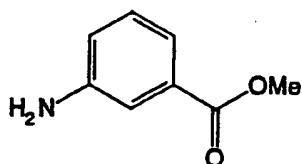
Other pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as, glycerol or sorbitol. The push-fit capsules can contain the active compounds in the form of granules that may be mixed with fillers such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds are preferably dissolved or suspended in suitable liquids, such as, fatty oils or liquid paraffin. In addition, stabilizers may be added.

Suitable formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form, for example, water-soluble salts and alkaline solutions. Especially preferred alkaline salts are ammonium salts prepared, for example, with Tris, choline hydroxide, bis-Tris propane, N-methylglucamine, or arginine. In addition, suspensions of the active compounds as appropriate oily injection suspensions can be administered. Suitable lipophilic solvents or vehicles include fatty oils, for example, sesame oil, or synthetic fatty acid esters, for example, ethyl oleate or triglycerides or polyethylene glycol-400 (the compounds are soluble in PEG-400). Aqueous injection suspensions can contain substances that increase the viscosity of the suspension, for example, sodium carboxymethyl cellulose, sorbitol, and/or dextran. Optionally, the suspension may also contain stabilizers.

The following examples are illustrative, but not limiting, of the method and compositions of the present invention. Other suitable modifications and adaptations of the variety of conditions and parameters normally encountered and obvious to those skilled in the art are within the spirit and scope of the invention.

### Example 1

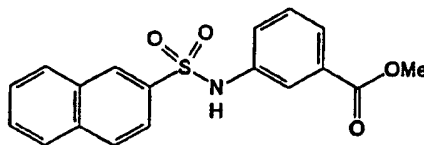
#### Preparation of Methyl 3-Aminobenzoate (6)



5 A mixture of methyl 3-nitrobenzoate (18.1 g, 0.10 mmol) in ethanol/  
tetrahydrofuran (9:1) and 1.8 g of 10% Pd/C was hydrogenated under a  
hydrogen atmosphere at atmospheric pressure and ambient temperature for  
24 hr. The reaction mixture was filtered through Celite (Celite is a  
10 registered trademark of the Johns-Manville Product Corporation for  
diatomaceous earth) and washed with ethanol. The solvent was removed *in vacuo* to give the title compound as a pale yellow solid (14.7 g; 97% yield)  
which was used as is in the next reaction. <sup>1</sup>H-NMR (200 MHz; CDCl<sub>3</sub>) δ  
7.43 (d, 1H, J = 7.6 Hz), 7.35 (t, 1H, J = 2.3 Hz), 7.25 (d, 1H, J = 2.3  
Hz), 7.19 (d, 1H, J = 7.7 Hz), 3.89 (s, 3H), 3.7 ppm (bs, 2H).

### Example 2

#### 15 Methyl 3-((2-Naphthalenyl)sulfonylamino)benzoate (7)

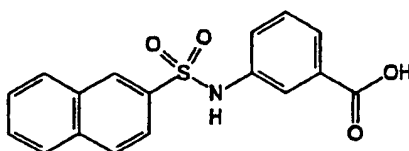


20 To 5.0 g (33 mmol) of methyl 3-aminobenzoate (6) in 70 mL of  
methylene chloride containing 4.0 mL (36 mmol) of N-methylmorpholine  
was added 7.49 g (33 mmol) of 2-naphthalenesulfonyl chloride. After  
stirring at room temperature overnight, the reaction mixture was quenched  
with 1 N HCl (100 mL). The suspension was dissolved in ca. 250 mL of

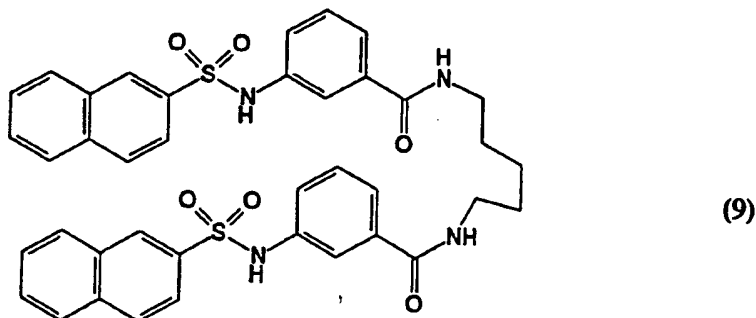
tetrahydrofuran and enough ether was added to induce phase separation. The organic extract was washed with saturated sodium chloride solution (2 x). The organic phase was dried ( $\text{MgSO}_4$ ), and concentrated to give 11.0 g (97% yield) of the title compound as a pale yellow solid:  $^1\text{H-NMR}$  (200 MHz;  $\text{DMSO-d}_6$ )  $\delta$  8.46 (s, 1H), 8.13 (t, 2H), 7.99 (d, 1H), 7.55-7.75 (m, 5H), 7.43 (dd, 2H), 7.38 (d, 1H), 3.79 ppm (s, 3H).

### Example 3

#### Preparation of 3-((2-Naphthalenyl)sulfonylamino)benzoic acid (8)



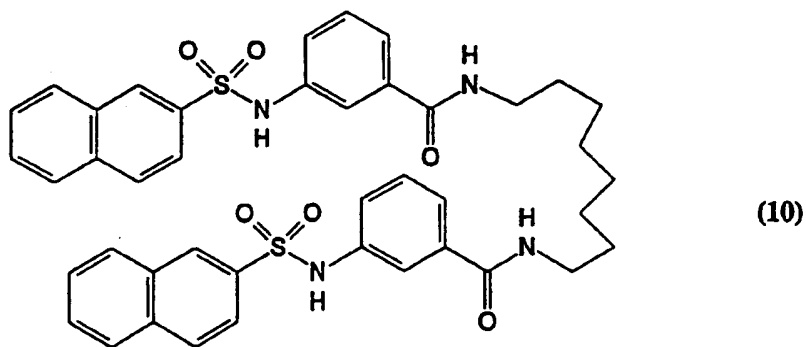
A solution of 10.8 g (31.7 mmol) of methyl 3-((2-naphthalenyl)sulfonylamino)benzoate (7) in 100 mL of 1 N NaOH was stirred at 50°C for 20 min. The reaction mixture was quenched with excess 2 N HCl, diluted with tetrahydrofuran to dissolve the suspension. Ether was added to induce phase separation. The organic extract was dried ( $\text{MgSO}_4$ ) and the solvent removed *in vacuo*. Trituration from ether/tetrahydrofuran/hexane gave 10.0 g of the title compound:  $^1\text{H-NMR}$  (200 MHz,  $\text{DMSO-d}_6$ )  $\delta$  8.45 (s, 1H), 8.13 (t, 2H), 7.99 (d, 1H), 7.54-7.81 (m, 5H), 7.77-7.43 ppm (m, 2H); Mass spectrum (MALDI-TOF) Calcd. for  $\text{C}_{17}\text{H}_{13}\text{NO}_4\text{S}$ : 328.1 (M + H) and 350.0 (M + Na). Found: 328.7 (M + H), 349.8 (M + Na).

*Example 4***Preparation of 1,5-di[3-(2-naphthalenylsulfonylamino)benzamido]pentane**

To a solution of 160 mg (0.469 mmol) of 3-((2-naphthalenyl)sulfonylamino)benzoic acid (8) in 3 mL of N,N-dimethylformamide was added 1 mL (0.5 mmol) of 0.5 M BOP (Castro's Reagent). Then 500 mL of diisopropylethylamine was added. After 5 min, the solution was transferred dropwise to a solution of 1,5-diaminopentane (55  $\mu$ L; 0.469 mmol). After 30 min, the reaction mixture was quenched with saturated sodium bicarbonate solution and extracted into ethyl acetate (3 x 3 mL). The organic phase was washed with saturated sodium bicarbonate solution (4 x 5 mL). The organic phase was concentrated and purified by silica gel chromatography using ethyl acetate/methylene chloride (1:1) to give the title compound:  $^1\text{H-NMR}$  (300 MHz; DMSO- $d_6$ )  $\delta$  10.5 (bs, 2 H), 8.43 (d, 2 H,  $J$  = 1.2 Hz), 8.36 (t, 2 H,  $J$  = 5.4 Hz), 8.10 (t, 4 H,  $J$  = 8.7 Hz), 7.97 (t, 2 H,  $J$  = 7.7 Hz), 7.77 (dd, 2 H,  $J$  = 1.8, 8.7 Hz), 7.59 - 7.71 (m, 6 H), 7.39 - 7.43 (m, 2 H), 7.25 (d, 2 H,  $J$  = 5.1 Hz), 3.16 (q, 4 H,  $J$  = 6.7 Hz), 1.45 (pentet, 4 H,  $J$  = 7.1 Hz), 1.25 ppm (2 H, pentet,  $J$  = 7.2 Hz).

### Example 5

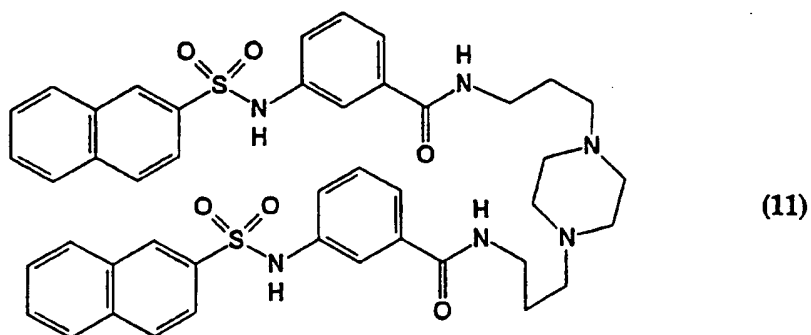
#### Preparation of 1,8-di[3-(2-naphthalenylsulfonylamino)benzamido]octane



In a manner identical to the procedure of Example 4 the title compound was prepared substituting 1,8-diaminooctane for 1,5-diaminopentane. Purification was achieved by crystallization from methylene chloride/ether/hexane/ethyl acetate:  $^1\text{H-NMR}$  (300 MHz,  $\text{DMSO-d}_6$ )  $\delta$  10.5 (bs, 2H), 8.44 (d, 2H, 1 Hz), 8.36 (t, 2H,  $J = 5.3$  Hz), 8.09 (t, 4H,  $J = 8.6$  Hz), 7.99 (d, 2H,  $J = 7.8$  Hz), 7.77 (dd, 2H,  $J = 1.8, 8.6$  Hz), 7.59-7.70 (m, 6H), 7.39-7.44 (m, 2H), 7.23-7.29 (m, 4H), 3.16 (q, 4H,  $J = 6.6$  Hz), 1.44 (br pentet, 4H), 1.24 ppm (br s, 8H).

### Example 6

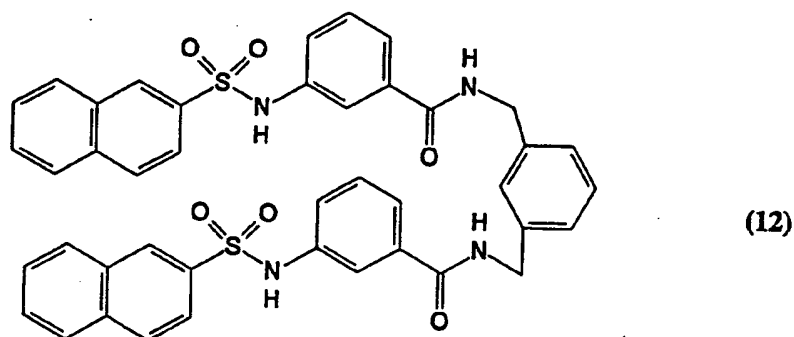
#### Preparation of 1,4-di-[3-(2-naphthalenylsulfonylamino)benzamido]piperazine



In a manner identical to the procedure of Example 4, the title compound was prepared substituting 1,4-bis(3-aminopropyl)piperazine for 1,5-diaminopentane. Purification was achieved by trituration from ethyl acetate/methylene chloride/ether/hexane to give the title compound: <sup>1</sup>H-NMR (300 Mz; DMSO-d<sub>6</sub>) δ 8.4 (d, 2H, J = 1 Hz), 8.37 (t, 2H, J = 5.4 Hz), 8.02-8.10 (m, 4H), 7.97 (d, 2H, J = 7.4 Hz), 7.75 (dd, 2H, J = 1.8, 8.6 Hz), 7.58-7.68 (m, 4H), 7.53 (s, 2H), 7.31-7.33 (m, 2H), 7.16 - 7.23 (m, 4H), 3.19 (q, 4H, 5.7 Hz), 2.23 - 2.28 (m, 10H), 1.59 ppm (pentet, 4H, J = 6.6 Hz).

### Example 7

#### Preparation of 1,3-di-[3-(2-naphthalenylsulfonylamino)benzamidoethyl]benzene



To a solution of 230 mg (0.7 mmol) of 3-((2-naphthalenyl)sulfonylamino)benzoic acid, (4) Castro's reagent (310 mg, 0.7 mmol), and triethylamine (0.3 mL) in anhydrous dimethylformamide (5 mL) was added *meta*-xylylenediamine (680 mg, 5 mmol). After stirring at ambient temperature for 3 h, the reaction mixture was diluted with 200 mL of ethyl acetate and then washed successively with saturated NaHCO<sub>3</sub> (2 x 50 mL), brine (3 x 50 mL), and 0.5 N HCl (4 x 50 mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated to give 100 mg (38% yield) of the

title compound as a white solid:  $^1\text{H-NMR}$   $\delta$  10.5 (bs, 2H), 8.96 (t, 2H,  $J = 6$  Hz), 8.44 (d, 2H,  $J = 1$  Hz), 8.09 (t, 4H,  $J = 8$  Hz), 7.98 (d, 2H,  $J = 8$  Hz), 7.77 (dd, 2H,  $J = 2, 9$  Hz), 7.60-7.70 (m, 6H), 7.45-7.50 (m, 2H), 7.10-7.28 (m, 6H), 4.37 (d, 4H). Mass spectrum Calcd. for  $\text{C}_{42}\text{H}_{24}\text{H}_4\text{O}_6\text{S}_2$ :  
5 777.9 (M + Na). Found: 778.0.

### Example 8

#### In Vitro Inhibition of Purified Enzymes

The ability of the compounds of the present invention to act as inhibitors of thrombin, factor Xa and plasmin catalytic activity was assessed  
10 by determining the concentration which inhibited enzyme activity by 50% using purified human enzymes. The concentration of added inhibitor that caused a 50% decrease in the initial rate of hydrolysis was defined as the  $\text{IC}_{50}$  value.

All assays are based on the ability of the test compound to inhibit the  
15 hydrolysis of a peptide *p*-nitroanilide substrate. In a typical experiment, appropriate substrate is prepared in DMSO, and diluted into an assay buffer consisting of 50mM HEPES and 130 mM NaCl at a pH of 7.5. The final concentration for each of the substrates is listed below. All substrate concentrations are at least 10 fold lower than  $K_m$  to insure inhibition is  
20 competitive. Test compounds are prepared as 1 mg/ml solutions in DMSO, and three additional 10-fold dilutions in DMSO are prepared. Enzyme solutions are prepared at the concentrations listed below in assay buffer.

In a typical  $\text{IC}_{50}$  determination, into each well of a 96 well plate is  
25 pipetted 280  $\mu\text{L}$  of substrate solution, 10  $\mu\text{L}$  of inhibitor solution, and the plate is allowed to thermally equilibrate at 37°C in a Molecular Devices Plate Reader for at least 10 minutes. Reactions are initiated by the addition of a 20  $\mu\text{L}$  aliquot of enzyme, and the absorbance increase at 405 nm is recorded for 15 minutes. Data corresponding to less than 10% of the total substrate hydrolysis is used in the calculations. The ratio of the velocity

(rate of the change in absorbance as a function of time) for a sample containing no inhibitor is divided by the velocity of a sample containing inhibitor, and is plotted as a function of inhibitor concentration. The inverse of the slope is the concentration of inhibitor which produces a 50% decrease in activity of the enzyme. This concentration is referred to as the  $IC_{50}$ .

### *Thrombin*

Thrombin activity was assessed as the ability to hydrolyse the substrate N-benzoyl-Phe-Val-Arg-p-nitroanilide (Bz-Phe-Val-Arg-pNa), and was obtained from Sigma Chemical Company (St. Louis, MO). Substrate solutions were prepared at a concentration of  $60 \mu M$  ( $60 \mu M < K_m = 1.2$  mM) in assay buffer. Final DMSO concentration was 0.3%. Purified human  $\alpha$ -thrombin was obtained from Enzyme Research Laboratories, Inc., and was diluted into assay buffer to a concentration of  $1.2 \mu M$ . Final reagent concentrations were: [thrombin] = 36 nM, [Bz-Phe-Val-Arg-pNa] = 66  $\mu M$ , [inhibitor] = 60 to 0.06  $\mu M$ .

### *Factor Xa*

Factor Xa activity was assessed as the ability to hydrolyse the substrate Bz-Ile-Glu-Gly-Arg-pNa, and was obtained from Sigma. Substrate solutions were prepared at a concentration of  $26 \mu M$  ( $26 \mu M < K_m = 1.3$  mM) in assay buffer. Final DMSO concentration was 0.3%. Activated factor Xa was obtained from Enzyme Research Laboratories, Inc., and was diluted into assay buffer to a concentration of  $1.2 \mu M$ . Final reagent concentrations were: [Factor Xa] = 10 nM, [Bz-Ile-Glu-Gly-Arg-pNa] = 26  $\mu M$ , [inhibitor] = 60 to 0.06  $\mu M$ .



*Plasmin*

Plasmin activity was assessed as the ability to hydrolyse the substrate Tos-Gly-Pro-Lys-pNa, and was obtained from Sigma. Substrate solutions were prepared at a concentration of 22  $\mu\text{M}$  ( $22\mu\text{M} \ll K_m = 240 \mu\text{M}$ ) in assay buffer. Final DMSO concentration was 0.3%. Purified human plasmin was obtained from Enzyme Research Laboratories Inc, and was diluted into assay buffer to a concentration of 1.2  $\mu\text{M}$ . Final reagent concentrations were: [plasmin]=15 nM, [Bz-Ile-Glu-Gly-Arg-pNa] = 26  $\mu\text{M}$ , [inhibitor] = 60 to 0.06  $\mu\text{M}$ .

The results obtained employing the compounds of Examples 4 through 7 are given in Table 1.

*Table 1*

Compound of Example	Factor Xa Inhibition $\text{IC}_{50}$ ( $\mu\text{M}$ )	Thrombin % Inhibition at 6 $\mu\text{M}$	Plasmin % Inhibition at 6 $\mu\text{M}$
4	3 $\mu\text{M}$	0%	0%
5	2.1 $\mu\text{M}$	20%	0%
6	5.2 $\mu\text{M}$	0%	0%
7	2.4 $\mu\text{M}$	20%	40%

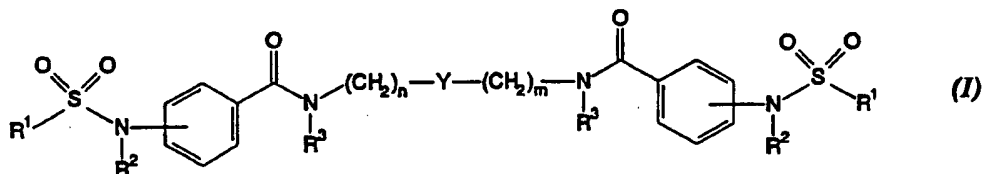
The results indicate that the compounds of the present invention, and specifically the compounds of Examples 4 through 7 are highly selective and potent inhibitors of factor Xa.

Having now fully described this invention, it will be understood to those of ordinary skill in the art that the same can be performed within a wide and equivalent range of conditions, formulations, and other parameters without affecting the scope of the invention or any embodiment thereof. All

patents and publications cited herein are fully incorporated by reference herein in their entirety.

*What Is Claimed Is:*

1. A compound having the Formula I:



wherein

5 each R<sup>1</sup> is independently one of alkyl, substituted alkyl, cycloalkyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl;

each R<sup>2</sup> and R<sup>3</sup> is independently one of hydrogen, alkyl, aryl or arylalkyl;

10 Y is a bond, or is one of  $-(CH_2)_p-$ , cycloalkyl, aryl or C<sub>2-10</sub>heterocycle; and

m, n and p are each independently 1 to 10.

2. The compound of claim 1, wherein

each R<sup>1</sup> is independently one of C<sub>6-12</sub>aryl or C<sub>1-8</sub>alkyl;

15 each R<sup>2</sup> and R<sup>3</sup> is independently one of hydrogen, C<sub>1-8</sub>alkyl or C<sub>6-12</sub>aryl;

Y is a bond, or is one of  $-(CH_2)_p-$ , C<sub>3-8</sub>cycloalkyl, C<sub>6-12</sub> aryl or a 4 to 7 membered ring heterocycle; and

m, n and p are each independently 1 to 5.

3. The compound of claim 2, wherein

20 each R<sup>1</sup> is the same and is one of phenyl, naphthyl or tetrahydronaphthyl;

each R<sup>2</sup> is the same and is one of hydrogen, C<sub>1-8</sub>alkyl, phenyl or naphthyl;

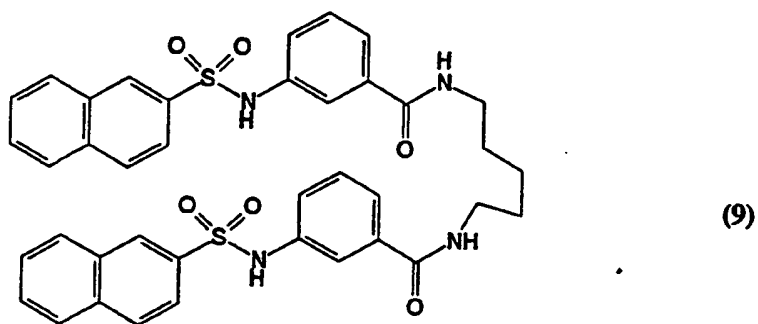
each  $R^3$  is the same and is one of hydrogen,  $C_{1-3}$ alkyl, phenyl or naphthyl;

Y is a bond, or is one of  $-(CH_2)_n-$ ,  $C_{3-8}$ cycloalkyl,  $C_{6-10}$ aryl or 1,4-piperazinyl; and

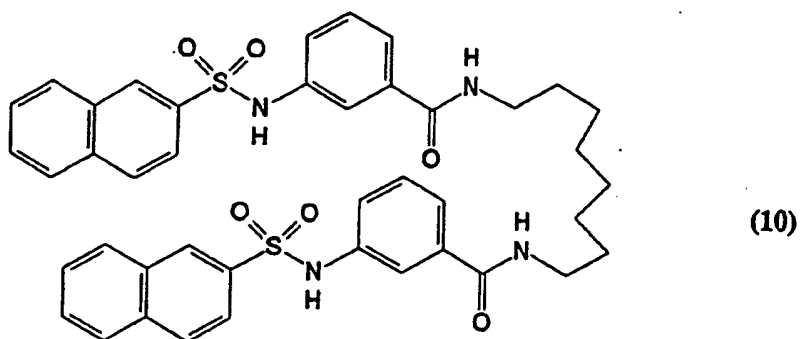
5

m, n and p are each independently 1 to 5.

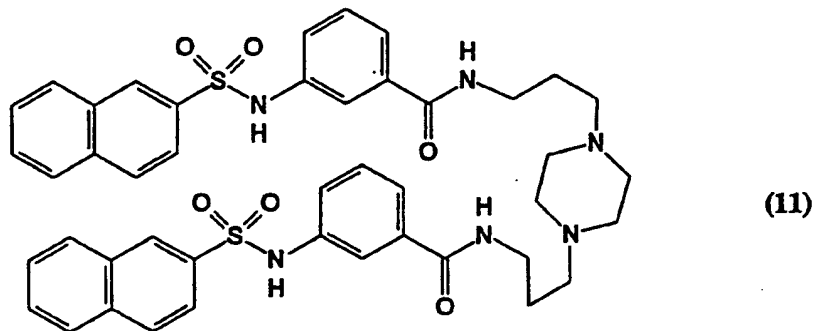
4. The compound of claim 3 having the structure:



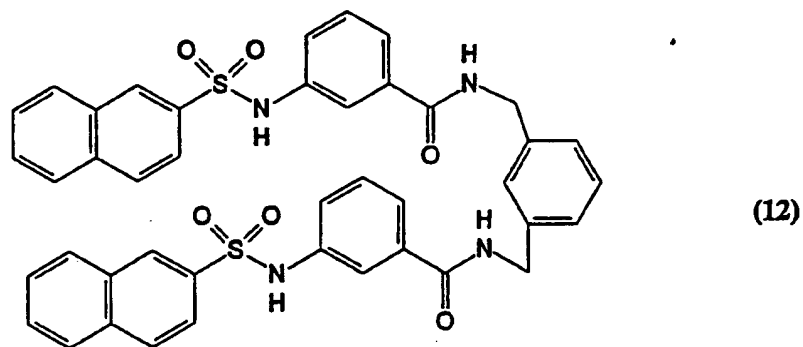
5. The compound of claim 3 having the structure:



6. The compound of claim 3 having the structure:



7. The compound of claim 3 having the structure:



5

8. A pharmaceutical composition comprising a compound of claim 1.

9. The pharmaceutical composition of claim 8 further comprising a pharmaceutically acceptable carrier or diluent.

10. A method of treating thrombosis, ischemia, stroke, restenosis or inflammation comprising administering to a mammal in need of said treatment a therapeutically or prophylactically effective amount of the compound of claim 1.

5

11. A method of treating thrombosis, ischemia, stroke, restenosis or inflammation comprising administering to a mammal in need of said treatment a therapeutically or prophylactically effective amount of one of the compounds of claims 4 through 7.

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US96/09308

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C07C 311/16; C07D 241/04, 295/00; A01N 43/60; A61K 31/18

US CL :564/82, 80; 544/398, 399, 400; 514/255, 602, 603

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 564/82, 80; 544/398, 399, 400; 514/255, 602, 603

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched  
The Merck Index (Eleventh Edition)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
APS, CAS ONLINE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,371,091 A (MISRA ET AL) 06 December 1994 (06.12.94), see entire document.	1-11
A	US 4,629,739 A (DAVEY ET AL) 16 December 1986 (16.12.86), see entire document.	1-11
A	US 4,544,654 A (DAVEY ET AL) 01 October 1985 (01.10.85), see entire document.	1-11
A	US 4,537,896 A (CLAESON ET AL) 27 August 1985 (27.08.85), see entire document.	1-11
A	US 4,977,168 A (BERNAT ET AL) 11 December 1990 (11.12.90), see entire document.	1-11



Further documents are listed in the continuation of Box C.



See patent family annex.

\*

Special categories of cited documents:

\*A\*

document defining the general state of the art which is not considered to be of particular relevance

\*E\*

earlier document published on or after the international filing date

\*L\*

document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

\*O\*

document referring to an oral disclosure, use, exhibition or other means

\*P\*

document published prior to the international filing date but later than the priority date claimed

\*T\*

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\*

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\*

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

\*Z\*

document member of the same patent family

Date of the actual completion of the international search

26 AUGUST 1996

Date of mailing of the international search report

02 OCT 1996

Name and mailing address of the ISA/US  
Commissioner of Patents and Trademarks  
Box PCT  
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

LILY LEDYNH

Telephone No. (703) 308-1235

**INTERNATIONAL SEARCH REPORT**

International application No.

PCT/US96/09308

**C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	STURZEBECKER et al. Synthetic Inhibitors of Bovine Factor Xa and Thrombin Comparison of Their Anticoagulant Efficiency. Thrombosis Research. 1989, Volume 54, No. 3, pages 245-252.	1-11
A	TAPPARELLI et al. Synthetic Low-molecular weight thrombin inhibitors: molecular design and pharmacological profile. Trends in Pharmacological Science. October 1993, Volume 14, pages 366-376.	1-11



# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US96/09308

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:  
1-11 (where Y is a bond,  $-(CH_2)-$ , cycloalkyl, aryl, heterocycle)
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☒  
☐

The additional search fees were accompanied by the applicant's protest.  
No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US96/09308

### BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack Unity of Invention because they are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for more than one species to be examined, the appropriate additional examination fees must be paid. The species are as follows:

- I. Species 1, wherein Y is a bond or  $-(CH_2)_p-$ , claims 1-9 and a method of treating thrombosis, claims 10 and 11.
- II. Species 2, wherein Y is cycloalkyl, claims 1-3, 8, 9 and a method of treating thrombosis, claim 10.
- III. Species 3, wherein Y is aryl, claims 1-3, 7-9 and a method of treating thrombosis, claims 10 and 11.
- IV. Species 4, wherein Y is heterocycle, claims 1-3, 6, 8, 9 and a method of treating thrombosis, claims 10 and 11.
- V. Method of treating ischemia, claims 10 and 11.
- VI. Method of treating stroke, claims 10 and 11.
- VII. Method of treating restenosis, claims 10 and 11.
- VIII. Method of treating inflammation, claims 10 and 11.

The following claims are generic: 1 and 8-11.

The species listed above do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: different Ys in Formula I result in different core structures which results in different special technical features for each grouping. Pursuant 37 CFR 1.475(d), the multiple methods are separated from the main invention.